1.1. INTRODUCTION

The Toll-like receptors (TLRs) are a class of pattern recognition molecules with unique functions in the innate and adaptive immune system ***(Netea et al., 2002).*** They are mammalian homologues of Toll, a type I transmembrane receptor first described in Drosophila, which in adult flies is involved in antifungal defence ***(Lemaitre et al., 1996*** *and* ***Miller, 2008).***

In human beings, 10 TLRs have been identified, each is activated by a different microbial component ***(Miller et al., 2005).*** The TLR structure includes an extracellular portion composed of leucine-rich repeats and an intracellular portion that shares homology with the intracytoplasmic domain of the IL-1 receptor ***(Baroni et al., 2006).***

TLRs play an essential role in the activation of innate immune response to microbial pathogens including bacteria, parasites, viruses and fungi and also interact with a variety of endogenous human ligands ***(Means et al., 2000).*** They impact on adaptive immune reactions and contribute to the initiation and maintenance of the inflammatory response to a multitude of potential microbial pathogens through recognition of pathogen-associated molecular patterns (PAMPs) ***(Cristofaro and Opal, 2006).***

These receptors are expressed on immune cells such as monocytes, dendritic cells and granulocytes. Importantly, TLRs are not only expressed by peripheral blood cells, but their expression has been demonstrated in airway epithelium and skin which are important sites of host-pathogen interaction ***(Mclnturff et al., 2005).***

The pattern of expression of TLRs in normal human skin was studied in the year 2000 followed by some others, where great variations were shown in the different studies. Keratinocytes (KCs) definitely express TLR1, 2, and 5 ***(Mempel et al., 2003; Kollisch et al., 2005*** *and* ***Miller et al., 2005),*** whereas controversy exists about the expression of TLR3, 4 and 9, which have been shown to be expressed in KCs by some authors ***(Miller et al., 2005).*** Recently, KCs have been shown to express TLRs 1 to 6 and 9 ***(Miller, 2008).***

As TLRs are instrumental in innate immune responses and influencing adaptive immunity, regulation of TLR expression at sites of some skin diseases may be important in their pathophysiology. This has been investigated in some studies on acne vulgaris, leprosy, atopic dermatitis, psoriasis, Lyme disease and others ***(Mclnturff et al., 2005).***

They also play a role in asthma, acute respiratory distress syndrome, cardiac ischemia, coronary artery disease, ventricular remodelling, vascular collapse, inflammatory bowel disease rheumatoid arthritis, acute tubular necrosis and fertility ***(Cristofaro and Opal, 2006).***

Furthermore, since TLRs are vital players in infectious and inflammatory diseases, they have been identified as potential therapeutic targets. The use of Imiquimod, a synthetic TLR agonist has already been established in treating anogenital warts. Studies have also demonstrated that it is effective in treating basal cell carcinoma, actinic keratosis, Bowen's disease and lentigo maligna ***(Mclnturff et al., 2005).***

Psoriasis is a common chronic inflammatory skin disease mediated by T-cells and characterized clinically by hyperproliferation of the epidermis ***(Baker et al., 1984*** and ***Boucock and Shannan, 2001).*** It is considered to be a genetically programmed disease of dysregulated inflammation, which is driven and maintained by multiple components of the immune system. The pathologic collaboration between innate immunity (mediated by antigen presenting cells (APCs) and natural killer (NK) T lymphocytes) and acquired immunity (mediated by T-lymphocytes) results in production of cytokines, chemokines and growth factors that contribute to the inflammatory infiltrate seen in psoriatic plaques ***(Gaspari, 2006).***

The exact etiology of psoriasis is unknown, although several microorganisms have been implicated as triggers capable of initiating or exacerbating the disease ***(Perez-Lorenzo et al., 2003).***

As TLRs play a key role in the innate immune response and in triggering inflammation, it is logical that they may be

involved in the psoriasis disease process, either in the recognition of exogenous products or in the recognition of self ligands ***(Gaspari, 2006),*** leading to the secretion of cytokines which activate acquired immunity via effects on T-cells, antigen presenting cells and endothelial cells ***(Bonifati and Ameglio, 1999).***

Further research on TLRs and their pathways will allow us to better understand their exact role in the pathophysiology of dermatological diseases as psoriasis. This can help in the discovery of potential therapeutic modalities that may alter the course of such dermatoses ***(Cristofaro and Opal, 2006).***

1.2. AIM OF THE WORK

The aim of this work is to investigate the expression of TLR1 and TLR2 on keratinocytes in normal skin and to determine whether modulation of these receptors occurs in lesional and non lesional skin of patients with psoriasis. It also aims to evaluate the correlation between the expression of these receptors and the disease severity. This may help to open up a new era in the therapeutic modalities of psoriasis.

2.1. PSORIASIS

Psoriasis is a common, inflammatory immune mediated disease of the skin and joints. Although seldom life threatening, psoriasis can be a debilitating chronic illness with pronounced physical, psychological, and social implications ***(Witman, 2001).*** It is characterised in most cases by sharply demarcated erythematous plaques with silvery scales which appear typically over the extensor surfaces, but the entire skin may be involved. Its course is usually relapsing and remitting with variation in severity and clinical manifestations even within the same individual ***(Godie, 2004; Campalani and Barker, 2005*** *and* ***Langley et al., 2005).***

2.1.1. Epidemiology:

It is estimated that the prevalence of psoriasis varies from 1-3%. There is a significant inter-racial and geographical variation in the distribution of the disease. Psoriasis tends to be more frequent at higher than lower latitudes, and more frequent in white than in black people or Asians ***(Kavli et al., 1985***; ***Green et al., 1996*** *and* ***Barker, 2001).***

Psoriasis can first appear at any age, from infancy to the eighth decade of life. Two peaks in the age of onset have been reported: one at 15-20 years of age and a second peak at 50-60 years ***(Burch and Rowell, 1981; Smith et al., 1993*** *and* ***Ferrandiz et al., 2002).*** As the disease is generally chronic and

persistent in nature, and because patients with psoriasis have a similar life expectancy compared to individuals without the disease, the prevalence of psoriasis increases with age ***(Bonifati et al., 1998).***

The prevalence of psoriasis is similar in both sexes ***(Gudmundsdottir et al., 1999),*** except for the palmoplanter pustular clinical subtype that is more common in women ***(Hellgren and Mobacken, 1971*** *and* ***Eriksson et al., 1998).***

There is an epidemiological association between psoriasis, especially severe forms, with certain diseases sharing certain pathogenic factors but targeting different organs, as arthritis and Crohn disease. Psoriasis also shares risk factors with coronary heart disease and occlusive vascular diseases ***(Sanz, 2007).***

2.1.2. Triggering factors:

Triggering factors both external and systemic, can elicit psoriasis in genetically predisposed individuals.

2.1.2.1. External triggering factors:

The koebner phenomenon describes the development of a skin condition or its worsening in an area of cutaneous injury. Psoriasis is one of several conditions characterized by this phenomenon, and as a result, will flare in areas of sunburn, surgical incisions, and traumatized skin. Psoriatic lesions can also be induced by morbilliform drug eruptions and viral

exanthemas. The lag time between the trauma and the appearance of skin lesions is usually 2-6 weeks ***(Witman, 2001*** *and* ***van de Kerkhof and Schalkwijk, 2008).***

2.1.2.2. Systemic triggering factors:

2.1.2.2.1. Infections:

Infections, especially bacterial infections, may induce or aggravate psoriasis. Streptococcal pharyngitis and other streptococcal infections often lead to a flare of guttate psoriasis especially in children and adolescents, but may also precipitate pustular psoriasis or exacerbate the plaque type. Appropriate antimicrobial therapy often hastens resolution of the psoriatic lesions in those patients ***(Skov and Baadgaard, 2000*** and ***Witman, 2001).***

Viral infections, in particular human immune deficiency virus (HIV), have been shown to aggravate psoriasis. The frequency of psoriasis is not increased in HIV positive patients, but the severity of the disease is greater in this population ***(Stern, 1995).***

2.1.2.2.2. Drugs:

Several medications have been implicated to trigger psoriasis including lithium, antimalarials, B-blockers and non-steroidals ***(Peters et al., 2000).*** Rapid with-drawl of systemic corticosteroids can induce pustular psoriasis as well as flares of plaque psoriasis ***(Tsankov et al., 2000).***

2.1.2.2.3. Endocrine factors:

Endocrinal factors as hypocalcemia have been reported to be a triggering factor for generalized pustular psoriasis. Pregnancy may alter disease activity leading to psoriasis improvement. Pregnant women, however, may develop pustular psoriasis known as impetigo herpetiformis, sometimes in association with hypocalcemia ***(van de Kerkhof and Schalkwijk, 2008).***

2.1.2.2.4. Psychogenic stress and climate:

Aggravating factors of psoriasis include stress and climate ***(Stern, 1995).*** Psychogenic stress has been associated with initial presentations of the disease as well as flares of pre-existing psoriasis ***(Gupta et al., 1989).*** Cold winter months are associated with increased flares of psoriasis, whereas warm sunny weather has an opposite effect (***(Witman, 2001).***

2.1.2.2.5. Alcohol consumption and smoking:

Increased alcohol consumption and smoking have been associated with psoriasis but they are not major risk factors ***(Higgens, 2000).***

2.1.3. Clinical features:

Psoriasis can be highly variable in morphology, distribution and severity. There is a spectrum of different clinical subtypes including plaque psoriasis, guttate psoriasis,

erythrodermic psoriasis, pustular psoriasis, inverse psoriasis and sebopsoriasis. These different forms may be localised or widespread and disabling. Further, psoriasis may have a variable course presenting as chronic, stable plaques or may present acutely with rapid progression and widespread involvement. Psoriasis may be symptomatic with patients complaining of intense pruritis or burning ***(Campalani and Barker, 2005*** *and* ***Langley et al., 2005).***

2.1.3.1. Plaque psoriasis (Psoriasis vulgaris):

It is the commonest form of psoriasis that accounts for around 80% of the diagnoses. It is characterised by well-demarcated erythematous plaques with loosely adherent silvery white scales which commonly affect elbows, knees, lumbosacral area, intergluteal cleft and scalp, yet, they may be found anywhere on the body. The amount of scaling varies among patients and even at different sites on a given patient. Removal of the psoriatic scales reveal tiny bleeding points (Auspitz sign) ***(Langley et al., 2005).***

As the plaques regress either spontaneously or in response to treatment, they often start to clear in the central area with a persisting erythematous margin, which confers an annular appearance. Plaque psoriasis exhibits clinical variation between patients regarding shape (annular, serpiginous, geographic), extent and response to treatment ***(Stern, 1997*** *and* ***Lebwohl, 2003).***

2.1.3.2. Guttate psoriasis:

It accounts for about 2% of the total cases of psoriasis. Patients with guttate psoriasis usually present with acute onset of small, round, erythematous scaly papules scattered mainly over the trunk and proximal extremities ***(Naldi et al., 2001*** *and* ***Campalani and Barker, 2005)***. It often occurs in children or young adults, and it is estimated that up to 80% of juvenile guttate psoriasis cases are preceeded by streptococcal infections ***(Barker, 1991; Mallon et al., 2000*** *and* ***Lebwohl, 2003).*** Guttate psoriasis is usually self-limiting, however a significant proportion eventually develops a more chronic form of psoriasis ***(Naldi et al., 2001*** *and* ***Campalani and Barker, 2005).***

2.1.3.3. Flexural (Inverse) psoriasis:

It affects the flexural areas, particularly the inframammary, perineal and axillary regions. Flexural lesions are devoid of scales and appear as erythematous, shiny moist well demarcated plaques occasionally confused with candidal and dermatophyte infections ***(Witman, 2001*** *and* ***Langley et al., 2005).***

Less than 3% of patients diagnosed with psoriasis present with a pustular eruption which can be either localised to palms and soles, or, less frequently, more generalised ***(Witman, 2001*** *and* ***Lebwohl, 2003).***

2.1.3.4. Palmoplantar pustular psoriasis (PPP):

It presents as clusters of sterile and painful yellow pustules over the ventral aspect of hands and feet especially over the thenar and hypothenar eminences of the palms and around the heels. It is frequently associated with psoriatic nail involvement. This condition is often resistant to therapy and leads to considerable debility and disability ***(Langley et al., 2005).***

PPP affects women more commonly than men with a ratio of 9:1. It presents mostly between the ages of 40 and 60 years, and has a striking association with smoking, either current or past in up to 95% of subjects ***(O'Doherty and Maclntyre., 1985).***

Approximately 25% of cases are associated with classic psoriasis vulgaris, but it is now believed that PPP may not be a form of psoriasis. This conclusion is derived from genetic studies showing no association with human leukocyte antigen (HLA) -Cw6 or other markers on chromosome 6p- which are linked to chronic plaque or guttate psoriasis ***(Asumalahti et al., 2003).***

2.1.3.5. Generalized pustular psoriasis (GPP):

GPP is rare and represents active, unstable disease. Precipitants of GPP include withdrawal of systemic or potent topical corticosteroids, hypocalcemia and infections. The patient presents with red, painful, inflammed skin studded with

monomorphic, sterile pustules which may coalesce to form sheets. Systemic symptoms are often present and include fever, arthralgia and malaise. Large lakes of pus can be formed when isolated sheets of pustules coalesce leading to disruption of the skin protective mechanisms and, if not treated; to sepsis, hypothermia and eventually death. Thus, patients with GPP frequently need to be admitted to the hospital for management ***(Campalani and Barker, 2005).***

2.1.3.6. Erythrodermic psoriasis:

It is a rare but life threatening condition where severe erythema and scaling can involve up to 100% of the skin surface. Fever, chills, malaise and pruritis often accompany it. Erythrodermic psoriasis may complicate plaque or pustular types or may be the initial manifestation of psoriasis. Erythroderma may impair the thermoregulatory capacity of the skin leading to hypothermia, high output cardiac failure, and metabolic changes including hypoalbuminaemia and anemia ***(Langley et al., 2005).***

2.1.3.7. Psoriatic arthritis:

Psoriasis can involve the musculoskeletal system (psoriatic arthritis). It occurs in 5-30% of patients with cutaneous psoriasis ***(Godie, 2004***) and can appear in 10-15% of patients before involvement of the skin. It is usually seronegative and can be manifested as mono- and asymmetrical oligoarthritis, arthritis of the distal interphalangeal joints,

rheumatoid arthritis-like changes, arthritis mutilans, and/or spondylitis ***(Green et al., 1996, De Rie et al., 2004*** *and* ***Godie, 2004).***

2.1.3.8. Nail psoriasis:

Nail involvement occurs in about 50% of psoriatic patients, and fingernails are more affected than toe nails ***(Scher, 1985).*** It has a tendency to occur in the presence of severe or long-standing skin disease and is often associated with psoriatic arthritis and scalp involvement. The commonest finding is small pits in the nail plate resulting from defective nail formation in the proximal portion of the nail matrix. The nail may also detach from the bed at its distal or lateral attachments, known as onycholysis. Orange yellow areas may be present beneath the nail plate and are termed "oil spots". The nail plate may also become thickened, dystrophic and discoloured. Yellow, keratinous material may collect under the nail plate and is known as subungual hyperkeratosis ***(De Rie et al., 2004; Campalani and Barker, 2005*** *and* ***Langley et al., 2005).***

2.1.3.9. Scalp psoriasis:

The scalp is one of the most common sites for psoriasis. The lesions often advance onto the periphery of the face, the retroauricular areas and the upper neck. Unless there is complete confluence, the individual lesions are discrete. The scales sometimes have an asbestos-like appearance and can be attached for some distance to the scalp hairs. Telogen effluvium

occasionally occurs within involved areas ***(van de Kerkhof and Schalkwijk, 2008).***